FORM PTO-1390 (REV 7-95)

U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. §371

ATTORNEY'S DOCKET NUMBER: KUTZ 3

U.S. APPLICATION NO (If known, see 37 CFR §1.5): 10/049442

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/EP00/06580	12 JULY 2000	12 AUGUST 1999

TITLE OF INVENTION

ORAL FORM OF ADMINISTRATION CONTAINING PROBIOTIC MICRO-ORGANISMS

APPLICANT(S) FOR DO/EO/US

BUG, Joachim, et al.

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ■ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. §371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. §371.
3. ☐ This express request to begin national examination procedures (35 U.S.C. §371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. §371(b) and PCT Articles 22 and 39(1).
4. ■ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. ■ A copy of the International Application as filed (35 U.S.C. §371(c)(2))
   a. ☐ is transmitted herewith (required only if not transmitted by the International Bureau).
   b. ■ has been transmitted by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ■ A translation of the International Application into English (35 U.S.C. §371(c)(2)).
7. ■ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. §371(c)(3))
   a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
   b. ■ have been transmitted by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☐ have not been made and will not be made.
8. ■ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. §371(c)(3)).
9. ■ An oath or declaration of the inventor(s) (35 U.S.C. §371(c)(4)).
10. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. §371(c)(5)).

Items 11. to 16. below concern document(s) or information included:

11. ☐ An Information Disclosure Statement under 37 C.F.R. §§1.97 and 1.98.
12. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 C.F.R. §§3.28 and 3.31 is included.
13. ■ A FIRST preliminary amendment.
14. ☐ A SECOND or SUBSEQUENT preliminary amendment.
15. ☐ A substitute specification.
16. ☐ A change of power of attorney and/or address letter.
17. ☐ Other items or information:

U.S. APPLICATION NO. (if known, see 37 CFR 1.5)	INTERNATIONAL APPLICATION NO	ATTORNEY'S DOCKET NUMBER
10/049442	PCT/EP00/06580	KUTZ 3

17. ☒ The following fees are submitted:

BASIC NATIONAL FEE (37 CFR §1.492 (a) (1) - (5)):

		CALCULATIONS PTO USE ONLY
Search Report has been prepared by the EPO or JPO	$890.00	
International preliminary examination fee paid to USPTO (37 CFR §1.482)	$710.00	
No international preliminary examination fee paid to USPTO (37 CFR §1.482) but international search fee paid to USPTO (37 CFR §1.445(a)(2))	$740.00	
Neither international preliminary examination fee (37 CFR §1.482) nor international search fee (37 CFR §1.445(a)(2)) paid to USPTO	$1040.00	
International preliminary examination fee paid to USPTO (37 CFR §1.482) and all claims satisfied provisions of PCT Article 33(2)-(4)	$100.00	

ENTER APPROPRIATE BASIC FEE AMOUNT =	$890.00	
Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 C.F.R. §1.492(e)).		

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total claims	13 - 20 =	0	x $ 18.00	$0.00	
Independent claims	2 - 3 =	0	x $ 84.00	$0.00	
MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+ $ 280.00		
TOTAL OF ABOVE CALCULATIONS =				$890.00	
Reduction of 1/2 for filing by small entity, if applicable. A Verified Small Entity Statement must also be					
SUBTOTAL =				$890.00	
Processing fee of **$130.00** for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 C.F.R. §1.492(f)).					
TOTAL NATIONAL FEE =				$890.00	
Fee for recording the enclosed assignment (37 C.F.R. §1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 C.F.R. §§3.28, 3.31). $40.00 per property.					
TOTAL FEES ENCLOSED =				$890.00	
				Amount to be refunded:	
				charged:	

a. ■ A check in the amount of $890.00 to cover the above fees is enclosed.

b. ☐ Please charge my Deposit Account No. 13-3402 in the amount of $ _____ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ■ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 13-3402. A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 C.F.R. §§1.494 or 1.495 has not been met, a petition to revive (37 C.F.R. §1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO: Customer Number 23,599

23599
PATENT TRADEMARK OFFICE

SIGNATURE

Anthony J. Zelano
NAME

27,969
REGISTRATION NUMBER

Filed: 12 FEBRUARY 2002
AJZ:kmo

APPLICATION DATA SHEET

APPLICATION INFORMATION

Application Type::	REGULAR
Subject Matter::	UTILITY
CD-ROM or CD-R?::	NONE
Title::	ORAL FORM OF ADIMINSTRATION CONTAINING PROBIOTIC MICRO-ORGANISMS
Attorney Docket Number::	kutz 3

INVENTOR INFORMATION

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CORRESPONDENCE INFORMATION

Correspondence Customer Number:: 23599

REPRESENTATIVE INFORMATION

Representative Customer Number:: 23599

DOMESTIC PRIORITY INFORMATION

Application::	Continuity Type::	Parent Application::	Parent Filing Date::
This Application	National Stage of	PCT/EP00/06580	07/12/00

FOREIGN PRIORITY INFORMATION

Application Number:	Country::	Filing Date::	Priority Claimed::
199 37 361.2	Germany	08/12/99	YES

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IN THE UNITED STATES DESIGNATED/ELECTED OFFICE

International Application No.	:	PCT/EP00/06580
International Filing Date	:	12 JULY 2000
Priority Date(s) Claimed	:	12 AUGUST 1999
Applicant(s) (DO/EO/US)	:	BUG, Joachim, et al.

Title: ORAL FORM OF ADMINISTRATION CONTAINING PROBIOTIC MICRO-ORGANISMS

PRELIMINARY AMENDMENT

Commissioner for Patents
Washington, D.C. 20231

SIR:

Prior to calculating the national fee, and prior to examination in the National Phase of the above-identified International application, please amend as follows:

IN THE CLAIMS:

3. (Amended) The tablet according to claim 1, characterized in that the probiotic microorganisms are lactobacilli, bifidus bacteris, or streptococci, preferably Lactobacillus casei, Lactobacillus acidophilus, Bifidobacterium bifidum, Bifidobacterium longum, and/or Lactobacillus plantarum.

4. (Amended) The tablet according to claim 1, characterized in that it contains from 10^3 to 10^{12}, preferably from 10^5 to 10^{11}, more preferably from 10^7 to 10^{10} probiotic microoganisms.

5. (Amended) The tablet according to claim 1, characterized in that the enteric coating essentially consists of shellac or of shellac and polyvinylpyrrolidone.

6. (Amended) The tablet according to claim 1, characterized in that the coating is comprised of at least two layers, one layer essentially consisting of hydroxypropylmethylcellulose, methylcellulose and/or polyvinylpyrrolidone, and/or one layer essentially consisting of shellac or shellac and polyvinylpyrrolidone.

8. (Amended) The tablet according to claim 5, characterized in that the amount of shellac is from 1 to 10 wt.-%, preferably from 1.5 to 6wt.-%, and more preferably from 2 to 3.5 wt.-%.

9. (Amended) The tablet according to claim 1, characterized in that it contains further nutritionally relevant additives, preferably vitamins, minerals, trace elements, roughage, enzymes, vegetable extracts, proteins, carbohydrates, and/or fats.

10. (Amended) The tablets according to claim 1, characterized in that ir contains additional adjuvants, particularly in its coating(s), preferably plasticizers, more preferably glycerol, Miglyol, mold wax, and/or acetylated monoglycerides.

11. (Amended) A process for producing the tablet according to claim 1, characterized in that the coating is coated from an aqueous solution and/or from an organic solution, preferably from an organic solution, and more preferably from am alcoholic solution.

Please add the following two claims:

12. An oral administration form containing at least one genus of probiotic microorganisms, characterized in that the administration form itself and/or the probiotic microorganisms has/have at least one enteric coating.

13. The oral administration form according to claim 12, characterized in that the oral administration form is a tablet , a coated tablet, a capsule, a granulate, or a powder, preferably at tablet, and more preferably a tablet, and more preferable a mulilayer tatablet.

REMARKS

The purpose of this Preliminary Amendment is to eliminate multiple dependent claims in order to avoid the additional fee. Applicants reserve the right to reintroduce claims to canceled combined subject matter.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached pages are captioned "**Version With Markings to Show Changes Made**".

Respectfully submitted,

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Filed: 12 February 2002

VERSION WITH MARKINGS TO SHOW CHANGES MADE

Claims 3 - 6 and 8-11 have been amended as follows:

3. (Amended) The tablet according to claim 1 ~~or 2~~, characterized in that the probiotic microorganisms are lactobacilli, bifidus bacteris, or streptococci, preferably Lactobacillus casei, Lactobacillus acidophilus, Bifidobacterium bifidum, Bifidobacterium longum, and/or Lactobacillus plantarum.

4. (Amended) The tablet according to claim 1 ~~or 3~~, characterized in that it contains from 10^3 to 10^{12}, preferably from 10^5 to 10^{11}, more preferably from 10^7 to 10^{10} probiotic microoganisms.

5. (Amended) The tablet according to ~~one or more of~~ claims 1 ~~to 4~~, characterized in that the enteric coating essentially consists of shellac or of shellac and polyvinylpyrrolidone.

6. (Amended) The tablet according to ~~one or more of~~ claims 1 ~~to 4~~, characterized in that the coating is comprised of at least two layers, one layer essentially consisting of hydroxypropylmethylcellulose, methylcellulose and/or polyvinylpyrrolidone, and/or one layer essentially consisting of shellac or shellac and polyvinylpyrrolidone.

8. (Amended) The tablet according to ~~one or more of~~ claims 5 ~~to 7~~, characterized in that the amount of shellac is from 1 to 10 wt.-%, preferably from 1.5 to 6wt.-%, and more preferably from 2 to 3.5 wt.-%.

9. (Amended) The tablet according to ~~one or more of~~ claims 1 ~~to 8~~, characterized in that it contains further nutritionally relevant additives, preferably vitamins, minerals, trace elements, roughage, enzymes, vegetable extracts, proteins, carbohydrates, and/or fats.

10. <u>(Amended)</u> The tablets according to ~~one or more of~~ claims 1~~ to 9~~, characterized in that ir contains additional adjuvants, particularly in its coating(s), preferably plasticizers, more preferably glycerol, Miglyol, mold wax, and/or acetylated monoglycerides.

11. <u>(Amended)</u> A process for producing the tablet according to ~~one or more of~~ claims 1~~ to 10~~, characterized in that the coating is coated from an aqueous solution and/or from an organic solution, preferably from an organic solution, and more preferably from am alcoholic solution.

Claims 12 and 13 are new and therefore no marked up version is necessary.

Claims:

1. A tablet containing at least one genus of probiotic microorganisms, characterized in that the tablet itself and/or the probiotic microorganisms has/have at least one enteric coating.

2. The tablet according to claim 1, characterized in that the tablet is a multilayer tablet.

3. The tablet according to claim 1 or 2, characterized in that the probiotic microorganisms are lactobacilli, bifidus bacteria, or streptococci, preferably *Lactobacillus casei*, *Lactobacillus acidophilus*, *Bifidobacterium bifidum*, *Bifidobacterium longum*, and/or *Lactobacillus plantarum*.

4. The tablet according to one or more of claims 1 to 3, characterized in that it contains from 10^3 to 10^{12}, preferably from 10^5 to 10^{11}, more preferably from 10^7 to 10^{10} probiotic microorganisms.

5. The tablet according to one or more of claims 1 to 4, characterized in that the enteric coating essentially consists of shellac or of shellac and polyvinylpyrrolidone.

6. The tablet according to one or more of claims 1 to 4, characterized in that the coating is comprised of at least two layers, one layer essentially consisting of hydroxypropylmethylcellulose, methylcellulose and/or polyvinylpyrrolidone, and/or one layer essentially consisting of shellac or of shellac and polyvinylpyrrolidone.

7. The tablet according to claim 6, characterized in that the coating is comprised of at least two layers arranged one on top of the other, the/one inner layer in the proximity of the core essentially consisting of hydroxypropylmethylcellulose, methylcellulose and/or polyvinylpyrrolidone,

and/or the/one outer, off-core layer essentially consisting of shellac or of shellac and polyvinylpyrrolidone.

8. The tablet according to one or more of claims 5 to 7, characterized in that the amount of shellac is from 1 to 10 wt.-%, preferably from 1.5 to 6 wt.-%, and more preferably from 2 to 3.5 wt.-%.

9. The tablet according to one or more of claims 1 to 8, characterized in that it contains further nutritionally relevant additives, preferably vitamins, minerals, trace elements, roughage, enzymes, vegetable extracts, proteins, carbohydrates, and/or fats.

10. The tablet according to one or more of claims 1 to 9, characterized in that it contains additional adjuvants, particularly in its coating(s), preferably plasticizers, more preferably glycerol, Miglyol, mold wax, and/or acetylated monoglycerides.

11. A process for producing the tablet according to one or more of claims 1 to 10, characterized in that the coating is coated from an aqueous solution and/or from an organic solution, preferably from an organic solution, and more preferably from an alcoholic solution.

10/049442
JC11 Rec'd PCT/PTO 12 FEB 2002

An Oral Administration Form

The invention relates to an oral administration form containing at least one genus of probiotic microorganisms, said administration form itself and/or said probiotic microorganisms having at least one enteric coating.

Many people, particularly in economically and industrially highly developed nations, frequently complain of temporary or chronic indigestion caused by a damaged or impaired intestinal flora. These "diseases of the affluent society" mostly are caused by stress situations, abuse of medications or drugs, consecutive symptoms of treatments with antibiotics, but also by malnutrition in many cases. Acute and severe symptoms can be treated using well-known drugs which may contain not only suitable pharmaceutical active substances but also appropriate natural enzymes or intestine-specific microorganisms.

However, in case of chronic, mild disorders of the intestinal tract not actually to be referred to as a disease, habitual consumption of suitable, selected foods or dietary supplementing preparations based on probiotic microorganisms frequently is sufficient to alleviate or eliminate the symptoms caused by an impaired or damaged intestinal flora. Even in case of an intact or healthy intestinal flora, the supply of probiotic microorganisms, particularly in combination with antioxidants, may have an immunostimulating effect.

For these reasons, yoghurt and curdled milk products become more and more popular. However, most of these products which are valuable in nutrition and include suitable probiotic microorganisms for this purpose are fresh products and

can only be stored under refrigeration, and even in this event, for just a few days.

Furthermore, there are products presenting suitable probiotic microorganisms in the form of a monopreparation. However, these products involve the disadvantage of lacking approval as food or food supplement in many countries because they do not contain any further nutrition-physiologically valuable substances such as minerals, fats, vitamins, carbohydrates, proteins, roughage, or trace elements.

Moreover, an average of only about 10% of the ingested probiotic microorganisms are capable of developing their healthful activity in the human or animal intestine. Therefore, a substantially larger amount of probiotic microorganisms than required in therapeutic terms has to be ingested in order to achieve a sufficiently high activity of these probiotic microorganisms in the human and animal intestine and thus, a healthful effect.

It was therefore the object of the invention to increase the activity of probiotic microorganisms in the human and/or animal intestine and thus, their healthful effect as well.

According to the invention, said object is accomplished by providing an oral administration form containing at least one genus of probiotic microorganisms, said administration form itself and/or said probiotic microorganisms having at least one enteric coating.

The oral administration preferably is a tablet, a coated tablet, a capsule, a granulate, or a powder, more preferably a tablet, with multilayer tablets being particularly preferred.

All those microorganisms are suitable as probiotic microorganisms which themselves normally occur in a healthy human or animal intestine and/or have a healthful effect on a healthy, impaired or diseased intestinal tract. For example, probiotic microorganisms promote the intestinal digestion of lactose in individuals exhibiting a lactose incompatibility, or promote more rapid convalescence from various diarrhetic diseases. Preferably, the probiotic microorganisms employed are lactobacilli, bifidus bacteria, or streptococci, with *Lactobacillus casei*, *Lactobacillus acidophilus*, *Bifidobacterium bifidum*, *Bifidobacterium longum*, and/or *Lactobacillus plantarum* being particularly preferred.

The amount of probiotic microorganisms in the oral administration form of the invention is to be selected in a way so as to ensure the desired healthful effect. The oral administration form of the invention preferably contains from 10^3 to 10^{12}, more preferably from 10^5 to 10^{11} probiotic microorganisms, with 10^7 to 10^{10} being particularly preferred. For stability with respect to number and activity of living microorganisms, the materials used, particularly the carrier material having embedded the probiotic microorganisms therein, advantageously have a water content as low as possible. The water content preferably is ≤3.0 wt.-%, more preferably ≤0.1 wt.-%, relative to the weight of the carrier material.

According to the invention, the oral administration form has at least one enteric coating. In a preferred embodiment, the oral administration form of the invention has at least one coating essentially consisting of shellac or of shellac and polyvinylpyrrolidone.

In another preferred embodiment, the oral administration form of the invention has at least one coating comprised of at least two layers, one layer essentially consisting of hydroxypropylmethylcellulose, methylcellulose and/or polyvi-

nylpyrrolidone, and/or one layer essentially consisting of shellac or of shellac and polyvinylpyrrolidone.

In another preferred embodiment, the oral administration form of the invention has at least one coating comprised of at least two layers, the/one inner layer in the proximity of the core essentially consisting of hydroxypropylmethylcellulose, methylcellulose and/or polyvinylpyrrolidone, and/or the/one outer, off-core layer essentially consisting of shellac or of shellac and polyvinylpyrrolidone.

The oral administration form of the invention preferably includes from 1 to 10 wt.-% shellac, more preferably from 1.5 to 6 wt.-%, relative to the total weight of the oral administration form, with 2 - 3.5 wt.-% being particularly preferred.

Essentially, the oral administration form of the invention has an enteric coating of at least such a size so as to entirely enclose the probiotic microorganisms.

Another preferred embodiment of the oral administration form includes probiotic microorganisms which themselves are provided with an enteric coating. To this end, the probiotic microorganisms are dried using various methods well-known to those skilled in the art and subsequently provided with at least one enteric coating.

Also, in addition to the enteric coating(s), the inventive oral administration form itself and/or the probiotic microorganisms optionally may have one or more additional coating(s). Preferably, this/these coating(s) serves/serve to achieve improved adherence of the enteric coating(s) and/or improved flavor, stability and/or optical appearance.

The coatings can be coated both from an aqueous solution and from an organic solution. As for the oral administration form of the invention, it is advantageous to coat the first coating, i.e., the first or inner layer close to the core from an organic solution because the probiotic microorganisms frequently are highly sensitive to moisture. It is particularly advantageous to coat the coatings or layers from an alcoholic solution of the coating materials.

In another preferred embodiment, the oral administration form of the invention includes further nutritionally relevant additives in addition to the probiotic microorganisms. Preferably, it includes vitamins, minerals, trace elements, roughage, enzymes, vegetable extracts, proteins, carbohydrates, and/or fats. In case the oral administration form includes nutritionally relevant additives, such as proteins, which already begin to undergo digestion in the stomach, it is important that these nutritionally relevant additives are at least not entirely enclosed by an enteric coating.

Depending on the nutritionally relevant additives used, it may be necessary to incorporate each of these and/or each of these and the probiotic microorganisms in the oral administration form of the invention in a way so as to avoid contact with each other. In a preferred fashion, this is accomplished by incorporating the nutritionally relevant additives and/or microorganisms in different layers of a multilayer tablet.

Preferred vitamins are vitamin A (β-carotene), vitamin C, vitamin E, B complex vitamins, and/or vitamin K. Particularly preferred vitamins are vitamin A, vitamin C and/or vitamin E. As a rule, the amounts of these vitamins depend on the recommended minimum required dose for the respective vitamin, but these amounts may also be exceeded by 50 - 200% on an average. A preferred range for vitamin C is between 50

and 300 mg, for vitamin E from 10 to 50 mg, for vitamin A ≤1.5 mg, and for the B complex vitamins from 10 μg to 20 mg.

Preferred minerals are edible inorganic or organic salts of sodium, potassium, calcium, magnesium, zinc, and/or iron, preferably present as carbonates, bicarbonates, phosphates, biphosphates, sulfates, bisulfates, chlorides, fluorides, citrates, and/or lactates. The amount of minerals relative to the total weight of the oral administration form preferably is from 20 to 40 wt.-%. The oral administration form of the invention preferably includes silicon, chromium, manganese, iodine, molybdenum, selenium, and/or copper as trace elements.

The oral administration form of the invention preferably includes soy bran, corn bran, wheat bran, and/or grain shot as roughage, with soy bran being particularly preferred. The amount of roughage relative to the total weight of the oral administration form preferably is from 2 to 50 wt.-%.

Preferred enzymes and coenzymes are lipases and/or proteases, and coenzyme Q, superoxide dismutase and/or glutathione peroxidase which promote the function of stomach and/or intestine and/or the metabolism. They may be incorporated in *per se* known amounts and in a *per se* known form.

In addition, the oral administration form includes further probiotic substances, preferably oligofructose and/or other oligosugars.

Preferably, the vegetable extracts are dry extracts from *Echinaceae*, bioflavonoids, polyphenols, phytoestrogens, and/or saponins.

Preferably, the oral administration form of the invention includes soy protein and/or whey protein as proteins,

and/or as fats those fats which contain polyunsaturated fatty acids.

Depending on the respective embodiment, the oral administration form of the invention may also include conventional adjuvants and additives. The selection of adjuvants and/or additives also depends on the food-related regulations in that country where the oral administration form of the invention is to be used. Particularly in its coating, the oral administration form of the invention preferably includes plasticizers such as glycerol, Miglyol, mold wax, and/or acetylated monoglycerides as additional adjuvants.

Starch (e.g., corn starch), talc, microcrystalline cellulose, lactose, highly dispersed silica, polyvinylpyrrolidone, and/or cellulose powder are used as additional adjuvants and/or additives e.g. in the tablets, multilayer tablets, coated tablets of the invention. As further components, carbohydrates such as mannitol, sorbitol, xylitol, glucose, sucrose, fructose, maltose, dextrose, maltodextrin, and/or kaolin, and/or cellulose derivatives such as methylcellulose, hydroxypropylcellulose and/or hydroxypropylmethylcellulose, and/or calcium carbonate, calcium, magnesium and/or glycerol stearate can be used as binders and/or antitack agents. In addition, the oral administration form of the invention may also include colorants, flavors and/or aromatic substances, as well as lubricants, antioxidants and/or stabilizers. On the one hand, the amount of these basic substances depends on the desired content of probiotic microorganisms, vitamins, enzymes, roughage, etc. and, on the other hand, on criteria determining the mechanical-physical properties of the oral administration form, such as hardness, compactibility, size, color, and/or shape.

The oral administration form of the invention can be produced according to methods well-known to those skilled in the art. For example, these methods are known from H. Sucker,

P. Fuchs, P. Speisser, "Pharmazeutische Technologie", Stuttgart, 1978; or K.H. Farmer, K.H. Frömming, C. Führer, "Pharmazeutische Technologie", Stuttgart, 1986. They are hereby incorporated by reference and thus, represent part of the disclosure.

The invention is also directed to methods of producing an oral administration form of the invention, characterized in that the coating(s) is/are coated from an aqueous solution and/or from an organic solution, preferably from an organic solution, and more preferably from an alcoholic solution.

The coatings can be coated using conventional methods well-known to those skilled in the art, e.g. tablet coating, spraying of solutions, dispersions or suspensions, or by powder coating procedures.

The oral administration form of the invention is advantageous in that a substantially smaller amount of probiotic microorganisms is required to achieve the desired healthful effect. As a result, it can be produced much more cheaply.

Examples

The following examples are intended to illustrate the invention without limiting the general idea thereof.

Example 1

A mixture of 65% bacteria preparation, 6% microcrystalline cellulose, 20% tricalcium phosphate, 2% glyceryl palmitostearate, 0.6% magnesium stearate, and 6.4% disintegrant was compacted together with a mixture of vitamins and

minerals on an eccentric press E1 by Fette Company or KS by Kilian Company to form an oblong tablet having a core weight of 1.35 g and the dimensions 20.0 mm × 8.8 mm × 7.0 mm. To produce the enteric coating, shellac was initially dissolved in ethanol with stirring and as soon as a clear solution was obtained, Miglyol was added to the solution and stirring was continued for another 15 minutes. This solution was subsequently coated onto the tablet, using a Schlick nozzle. The process parameters were selected in a way so as to obtain homogeneous film coating. The amount of shellac was 2.1 wt.-% relative to the weight of the core, corresponding to 4.5 mg per cm^2 tablet surface.

Example 2

A mixture of 10% bacteria preparation, 33% lactose, 48.4% microcrystalline cellulose, 2% glyceryl palmitostearate, 0.6% magnesium stearate, and 6.0% disintegrant was compacted together with a mixture of vitamins and minerals on a rotary pelleter by Manesty Company to form an egg-shaped tablet having a core weight of 1.0 g and the dimensions 18.0 mm × 8.8 mm × 7.2 mm. Thereafter, a film of hydroxypropylmethylcellulose was coated thereon by spraying an ethanolic solution. The amount of coated hydroxypropylmethylcellulose was 0.8 wt.-% relative to the weight of the core, corresponding to 1.4 mg per cm^2 tablet surface. Then, also by spraying an ethanolic solution, another enteric coating comprised of shellac, polyvinylpyrrolidone and acetylated monoglycerides was coated over this first layer of hydroxypropylmethylcellulose. The amount of shellac was between 0.25 and 0.35 wt.-% relative to the weight of the core, corresponding to 4.5 mg/cm^2 - 6.3 mg/cm^2 tablet surface. The amount of acetylated monoglycerides and polyvinylpyrrolidone was 14.2 wt.-% each, relative to the amount of shellac employed.

Example 3

A mixture of 65% bacteria preparation, 6% microcrystalline cellulose, 20% tricalcium phosphate, 2% glyceryl palmitostearate, 0.6% magnesium stearate, and 6.4% disintegrant was compacted together with a mixture of vitamins and minerals on a rotary pelleter by Hata Company to form an egg-shaped tablet having a core weight of 1.35 g and the dimensions 21.0 mm × 10.0 mm × 8.0 mm. Thereafter, a film of hydroxypropylmethylcellulose and glycerol or Miglyol was coated thereon by spraying an ethanolic solution. The amount of coated hydroxypropylmethylcellulose was 0.8 wt.-% relative to the weight of the core, corresponding to 1.48 mg per cm^2 tablet surface. The amount of glycerol or Miglyol was 10 wt.-% relative to the amount of hydroxypropylmethylcellulose employed. Likewise by spraying an ethanolic solution, another enteric coating comprised of shellac, polyvinylpyrrolidone and acetylated monoglycerides was coated over this first layer of hydroxypropylmethylcellulose. The amount of coated shellac was between 0.3 and 0.5 wt.-% relative to the weight of the core, corresponding to 4.1 mg/cm^2 - 6.8 mg/cm^2 tablet surface. The amount of acetylated monoglycerides and polyvinylpyrrolidone was 14.2 wt.-% each, relative to the amount of shellac employed.

Claims:

1. An oral administration form containing at least one genus of probiotic microorganisms, characterized in that the administration form itself and/or the probiotic microorganisms has/have at least one enteric coating.

2. The oral administration form according to claim 1, characterized in that the oral administration form is a tablet, a coated tablet, a capsule, a granulate, or a powder, preferably a tablet, and more preferably a multi-layer tablet.

3. The oral administration form according to claim 1 or 2, characterized in that the probiotic microorganisms are lactobacilli, bifidus bacteria, or streptococci, preferably *Lactobacillus casei*, *Lactobacillus acidophilus*, *Bifidobacterium bifidum*, *Bifidobacterium longum*, and/or *Lactobacillus plantarum*.

4. The oral administration form according to one or more of claims 1 to 3, characterized in that it contains from 10^3 to 10^{12}, preferably from 10^5 to 10^{11}, more preferably from 10^7 to 10^{10} probiotic microorganisms.

5. The oral administration form according to one or more of claims 1 to 4, characterized in that the enteric coating essentially consists of shellac or of shellac and polyvinylpyrrolidone.

6. The oral administration form according to one or more of claims 1 to 4, characterized in that the coating is comprised of at least two layers, one layer essentially consisting of hydroxypropylmethylcellulose, methylcellulose and/or polyvinylpyrrolidone, and/or one layer

essentially consisting of shellac or of shellac and polyvinylpyrrolidone.

7. The oral administration form according to claim 6, characterized in that the coating is comprised of at least two layers arranged one on top of the other, the/one inner layer in the proximity of the core essentially consisting of hydroxypropylmethylcellulose, methylcellulose and/or polyvinylpyrrolidone, and/or the/one outer, off-core layer essentially consisting of shellac or of shellac and polyvinylpyrrolidone.

8. The oral administration form according to one or more of claims 5 to 7, characterized in that the amount of shellac is from 1 to 10 wt.-%, preferably from 1.5 to 6 wt.-%, and more preferably from 2 to 3.5 wt.-%.

9. The oral administration form according to one or more of claims 1 to 8, characterized in that it contains further nutritionally relevant additives, preferably vitamins, minerals, trace elements, roughage, enzymes, vegetable extracts, proteins, carbohydrates, and/or fats.

10. The oral administration form according to one or more of claims 1 to 9, characterized in that it contains additional adjuvants, particularly in its coating(s), preferably plasticizers, more preferably glycerol, Miglyol, mold wax, and/or acetylated monoglycerides.

11. A process for producing the oral administration form according to one or more of claims 1 to 10, characterized in that the coating is coated from an aqueous solution and/or from an organic solution, preferably from an organic solution, and more preferably from an alcoholic solution.

Abstract:

The invention relates to an oral administration form containing at least one genus of probiotic microorganisms, said administration form itself and/or said probiotic microorganisms having at least one enteric coating.

Docket No.
Merck

Declaration and Power of Attorney For Patent Application
English Language Declaration

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name,

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled

Oral form of administration containing probiotic micro-organisms

the specification of which

(check one)

☐ is attached hereto.
☒ was filed on 12 July 2000 as United States Application No. or PCT International Application Number PCT/EP00/06580
and was amended on _____
(if applicable)

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, Section 1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, Section 119(a)-(d) or Section 365(b) of any foreign application(s) for patent or inventor's certificate, or Section 365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate or PCT International application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application(s)			Priority Not Claimed
199 37 361.2 (Number)	Germany (Country)	12 August 1999 (Day/Month/Year Filed)	☐
_____ (Number)	_____ (Country)	_____ (Day/Month/Year Filed)	☐
_____ (Number)	_____ (Country)	_____ (Day/Month/Year Filed)	☐

I hereby claim the benefit under 35 U.S.C. Section 119(e) of any United States provisional application(s) listed below:

(Application Serial No.)	(Filing Date)

I hereby claim the benefit under 35 U.S.C. Section 120 of any United States application(s), or Section 365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States of PCT International application in the manner provided by the first paragraph of 35 U.S.C. Section 112. I acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, C.F.R., Section 1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application:

(Application Serial No.)	(Filing Date)	(Status) (patented, pending, abandoned)

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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